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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Weers et al.
Appl. No.	:	09/851,226
Filed	:	May 8, 2001
For	:	PHOSPHOLIPID-BASED POWDERS FOR DRUG DELIVERY
Examiner	:	Wells, L.

Group Art Unit 1617

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

11/25/2002
(Date)

Karen J Moir
Karen Moir

#12 Supp 1-15-03
Karen J Moir

DECLARATION OF DR. JEFFRY WEERS UNDER 37 C.F.R. §1.132

Dear Sir:

1. I am currently employed by Inhale Therapeutic Systems, Inc. (Inhale) and hold the position of Director of Advanced Particle Research, Technical Leader, PulmoSphere ® Technology. I have attached hereto a copy of my curriculum vitae which demonstrates that I am an expert in the field of aerosolized medications and have particular knowledge and understanding of the formulation and processing challenges in developing phospholipid compositions of sufficient physical and chemical stability to be suitable for formulating as spray dried powders intended for administration via inhalation.

2. I am co-inventor and have reviewed the above-identified patent application, the claims being presented by amendment simultaneously with this amendment, the office actions which have been entered in this case, and the references relied upon by the Examiner, and it is my opinion that the invention, as claimed, would not have been obvious to one of ordinary skill in the art over any combination of references cited by the Examiner and any other combination of references of which I am aware due to the unexpected benefits relating to physical stability and dispersibilty achieved through the use of a very hygroscopic salt, such as calcium chloride, together with saturated phospholipids as discussed in detail below.

3. I am familiar with the level of skill of one of ordinary skill in the art in the field of aerosolizable pharmaceutical formulations used in dry powder inhalers ("DPIs"). Typically, the individual would have at least a bachelor's degree in pharmaceutics or related field, but more often he or she would have an advanced degree such as a Ph.D. In addition, he or she would have at least eight years hands on experience in working with dry powder formulations. Furthermore, he or she would be familiar with at least some of the many articles written by John Patton, Peter Byron, Richard Dalby, Andy Clark, and others, as well as the Respiratory Drug Delivery Proceedings edited by Dr. P. R. Byron for CRC Press, Inc. One of ordinary skill in the art would recognize the many challenges that have confronted the DPI industry.

4. It would be recognized by one of ordinary skill in the art that preparing dry powder formulations of a size suitable for inhalation and having the requisite physical and chemical stability is a difficult and challenging hurdle. Ideally from a product quality standpoint, the T_g or T_m should be much greater (ca. $t_m - t_s > 50°C$) then the storage temperature (t_s), typically room temperature, to ensure good long-term stability. Spray-dried powders with a Tm less than 10 °C form highly cohesive powders that appear agglomerated (melted/annealed, note page 3, line 1 of the present specification). Hence, the data collected in our study discussed below that shows that even in the presence of calcium ions, Tm values for unsaturated phospholipids are <10 °C thereby supporting the assertion that the addition of calcium ions to unsaturated phospholipids does little to improve their ability to provide storage stable powders for pharmaceutical applications.

5. In making the obviousness rejections, the Examiner relies heavily upon the teachings in Materne et al. stating that it would be obvious to substitute the calcium phophatidylcholine of Materne et al. for the phospholipids of either Hanes et al. or Weers et al. A careful read of the Materne reference describes the use of calcium chloride in combination with unsaturated phosphatidylcholine for a process for producing a product of high purity and better handling characteristics. Although not explicitly stated in Materne, it is clear to one of ordinary skill in the art that the phosphatidylcholines of Materne are unsaturated because of their physicochemical properties and appearance as

described therein. For example, Materne describes phosphatidylcholines as plastic materials of low stability, which are difficult to process and handle. This is an accurate description of unsaturated phosphatidylcholines with a Tm < 10 °C, where particles fuse into large agglomerates due to temperature or moisture induced aggregation. Unsaturated phosphatidylcholines are also unstable due to oxidative processes involving the double bonds and must typically be stored at -20°C to maintain stability.

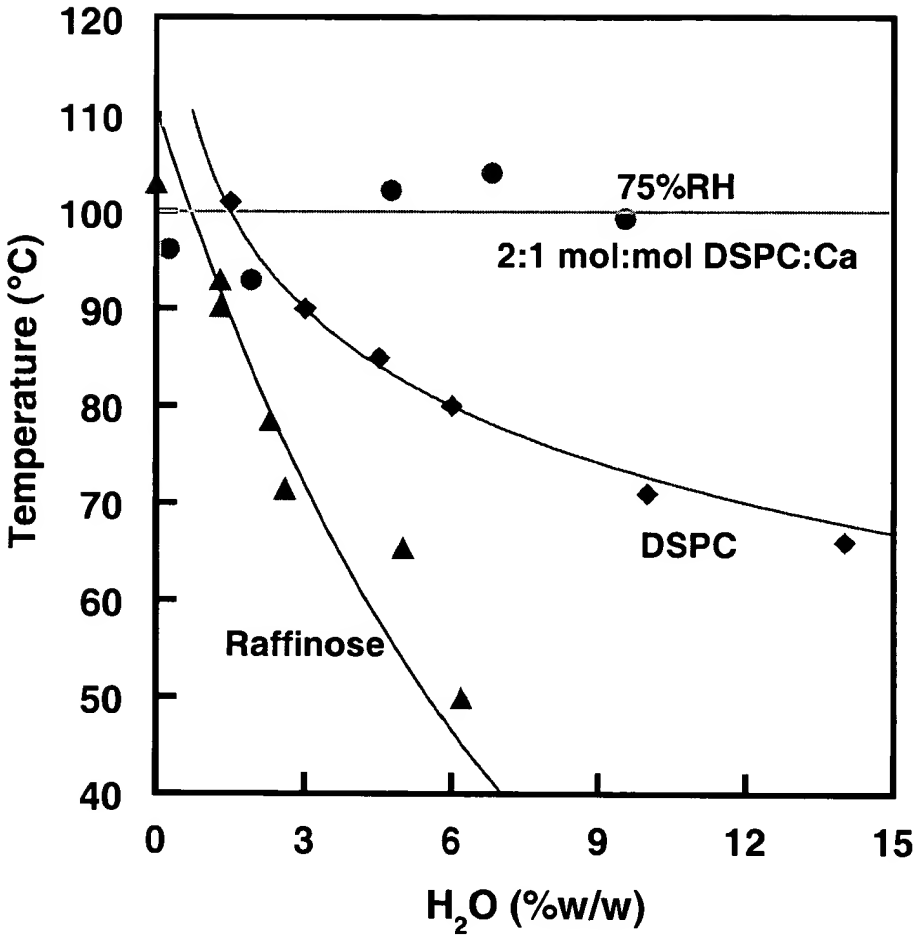
6. In contrast, the saturated phosphatidylcholines of the present invention arrive from vendors as flowable powders (i.e., no plastic component), which are stable chemically since they contain no double bonds that can be oxidized. Saturated phosphatidylcholines are not difficult to handle under normal ambient conditions. As well, Materne describes the phosphatidylcholines as having a yellow color. The yellow color is a result of oxidative processes involving the double bond presented in unsaturated materials. In contrast, saturated phosphatidylcholines are white in appearance. However, the phosphatidylcholines of Materne are intended for use in preparing phosphatidylcholine raw material and not as a final pharmaceutical product where the physical properties of the lipids is more demanding.

7. It has been found that the T_m of the phospholipid is critical in obtaining phospholipid-based dry powders that both flow well, and are readily dispersible from passive dry powder inhalers (DPIs) and metered dose inhalers (MDIs). Phospholipids with T_m values less than 10°C (e.g. egg PC or any unsaturated lipids), form highly cohesive powders following spray drying. Inspection of the powders via scanning electron microscopy reveals highly agglomerated particles with surfaces that appear to have been melted or annealed. One key formulation aspect of the invention is the use of calcium ions. When bound to the phosphate portion of the phosphatidylcholine headgroup, calcium ions help to condense lipid packing, thereby decreasing headgroup hydration, and making the phospholipid more crystalline in nature. This translates into spray-dried particles that are much less sensitive to variations in moisture content as determined by variations in T_m, and powders with good flow properties. This phenomenon has been applied to saturated phosphatidylcholines, but not to unsaturated species. The inability of calcium ions to

have any significant affect on the thermal properties of unsaturated phosphatidylcholines is most likely due to the highly disordered packing of these lipid species. It is this disorder that renders these materials too cohesive, plastic and poor flowing for DPI and MDI applications. The small increases in Tm observed are of no practical significance for inhalation applications. In addition, these formulations are sensitive to both elevated temperature and moisture. As a result, they are not suitable for dry powder formulations intended for inhalation.

8. It would be further recognized by one of ordinary skill in the art that the spray-drying process used to create such particulate formulations creates amorphous particles that must be protected from excursions in moisture. For example, amorphous glasses of raffinose show dramatic decreases in their order to disorder transition (i.e., the glass transition temperature (T_g)) with increases in moisture content. Similarly, phospholipids such as phosphatidylcholine show decreases in their order to disorder transition (gel to liquid crystal phase transition, T_m) with increasing moisture content, to the point where fully hydrated DSPC has a Tm of 56°C. This is further highlighted with reference to Fig. 1 below. Fig. 1 depicts a plot of the order to disorder transitions as a function of water content in the powder for three spray-dried powders. Raffinose, which forms an amorphous glass, exhibits a dramatic decrease in Tg with increasing moisture content. Spray-dried DSPC also exhibits a significant decrease in the gel to liquid crystal phase transition temperature with moisture content, while a 2:1 mol:mol ratio mixture of DSPC:Ca does not. The DSPC:Ca mixture maintains its high Tm value even under storage conditions of 75% relative humidity (Tm ≈100°C). This is approximately 60°C above the storage temperature of the powder.

Fig. 1



9. In response to the Examiner's statements above, I have performed comparative experiments which examine the effect of calcium chloride on the gel to liquid crystal transition temperature of both saturated and unsaturated phospholipids. As seen from the experimental results, the addition of calcium chloride to saturated phospholipids provided a significant increase in the gel to liquid crystal transition temperature, thus improving the physical stability of the particulate powders, while no such benefit was achieved through the addition of calcium chloride to unsaturated phospholipids. As well, the addition of calcium chloride unexpectedly decreases the sensitivity of the powders to

increases in relative humidity. Based upon these results and for the reasons set forth above, it is my opinion that the unexpected benefits attributed to the addition of calcium chloride to saturated phospholipids would not have been obvious to one of ordinary skill in the art at the time of the invention. A detailed discussion of the experimental procedure and results follows below.

10. Materials

Two sources of unsaturated phosphatidylcholines were examined to determine the physicochemical characteristics of spray-dried powders comprised of unsaturated phosphatidylcholines and calcium chloride. Both sources represent typical raw material preparations available for the food or pharmaceutical industry. DSPC was used as the model saturated phospholipid.

Egg Lecithin[1,3] –	Avanti Polar Lipids –	Part No. 141601
Egg Phosphatidylcholine[2,3] -	Avanti Polar Lipids –	Part No. 830051
DSPC -	Genzyme Corp. -	Part No. LP-04-076
Calcium Chloride dihydrate	EM Science	
Deionized water		

[1] *Egg Lecithin is obtained from fresh egg yolks that are extracted with organic solvents. The extract is precipitated with acetone and then extracted with diethyl ether. The resulting extract is dried yielding a >95% PC content.*

[2] *Egg PC is obtained from fresh egg yolks that are extracted with organic solvents. The non-polar lipids (triglycerides, etc) are then removed using a series of chromatography columns. The resulting fraction is dried yielding a >99% PC content.*

[3] *The fatty acid composition of Egg PC is as follows: 34% palmitic (16:0), 1.7% palmitoleoyl (16:1), 11% stearic (18:0), 32% oleoyl (18:1), 18% linoleoyl (18:2) and 3.3 % arachidonyl (22:4).*

11. Particle Preparation

Dry phospholipid particles containing long-chain phosphatidylcholines (PC) and varying amounts of calcium chloride were manufactured using a spray-drying process. Calcium levels were adjusted as mole ratio equivalents relative to the PC present, with

Calcium/PC (mol/mol) = 0 and 0.5. Accordingly, 1 g of PC and 0 or 0.91 g of calcium chloride dihydrate were dispersed in approximately 27.3 mL of hot deionized water (T = 60-70° C) using an Ultra-Turrax T-25 mixer at 8,000–10,000 rpm for 2 to 5 minutes. The resulting PC dispersion was then spray-dried with a Buchi B-191 Mini Spray-Drier (Flawil, Switzerland), equipped with a modified 2-fluid atomizer under the following conditions: inlet temperature = 85 °C; outlet temperature = 58°-61 °C; pump = 1.9 ml/ min; atomizer pressure = 60-65 psig; atomizer flow rate = 30–35 cm. The aspiration flow (70–90%) was adjusted to maintain a Venturi manifold pressure of 1.7 to 2.0 inches of water. The spray-dried phospholipid particles were collected using the standard Buchi cyclone separator.

12. Dry Phospholipid Formulations

Lot #	Phosphatidylcholine	Calcium Chloride
A	1.0 g Egg Lecithin	None
B	1.0 g Egg Lecithin	0.091 g
C	1.0 g Egg Phosphatidylcholine	None
D	1.0 g Egg Phosphatidylcholine	0.091 g
E	1.0 g DSPC	None
F	1.0 g DSPC	0.091 g

13. Characterization Methods

The raw materials prior to spray drying and the resulting spray dried powders were analysed using the following testing scheme:

Test	**Phospholipid Raw Material**	**Spray-Dried Phospholipid Particles**
Appearance (Visual)	X	X
Morphology (SEM)		X
T_m (DSC)	X	X
Particle Size Distribution (Laser Diffraction)		X
Production Yield		X

14. Visual Appearance

No discrete particles were observed when the unsaturated phospholipids were viewed via optical microscopy. Powders produced with naturally derived PCs had a yellow or greyish color, waxy appearance and poor handling characteristics. The DSPC powders were white in appearance and existed as a finely divided free flowing powder.

15. Morphology (SEM)

The morphological assessment (SEM) and particle distribution measurements were not performed due to the poor handling properties of the materials produced from the egg lecithin and egg phosphatidylcholine raw materials. These materials existed as waxy, plastic materials that could not be analysed by these techniques.

16. DSC Analysis

The solid state characteristics of the phospholipid materials were determined via differential scanning calorimetry (DSC). Accordingly, 0.5 to 2 mg of dry powder were weighed into aluminum sample pans and hermetically sealed. Each sample was analysed on a model 2920 DSC (TA Instruments) under the following conditions: equilibration at –20 °C, and 2 °C/min ramp to 150 °C modulated +/- 1 °C every 60 sec. The phospholipid Tm is defined as the peak maxima of the first endothermic transition from each reversing heat flow thermogram.

Sample preparation for paste like samples (All, except DSPC-containing formulations)

About 9 to 11 mg of sample was placed into an aluminum DSC pan and gently packed to form a uniform layer on the bottom of the pan (Catalog numbers 900 793.901 (pan) and 900 794.901 (lid)). The DSC pan was hermetically sealed using a sample encapsulation press (part # 900680.902).

Sample preparation for powder (All DSPC-containing formulations)

To increase the sample mass and sensitivity, a disc of powder was prepared using a 5/32" diameter custom stainless steel press. Gentle pressure was applied to produce a 9 to 11 mg disc that fit inside the aluminum DSC pan (part numbers 900 793.901 (pan) and 900 794.901 (lid)). The DSC pan was hermetically sealed using a sample encapsulation press (part # 900680.902).

The DSC thermogram of each powder was measured using a DSC-Q1000 instrument made by TA Instruments (New Castle, Delaware). Helium was used as a purge gas at 30 cm^3/minute.

The samples were loaded using an auto-sampler system. Prior to the runs, the DSC software program was setup with all sample parameters entered, and samples were placed in the auto-sampler in appropriate pan positions. In a DSC experiment, the sample was first cooled to –80°C, held isothermally for 5 minutes, and then heated at 2°C/minute to 130°C. The heating rate was *not* modulated. Prior to these experiments, the instrument was calibrated for temperature and enthalpy using an indium reference standard; the calibration was then verified using an independent experiment.

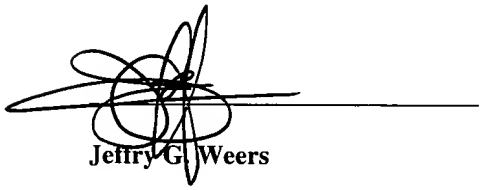
17. DSC Results

Summary of DSC T_m results. Peaks are numbered sequentially from lowest to highest T_m. The T_m values for the largest (main) peak are shown in red, boldface type. Due to the presence of overlapping peaks, choosing the main peak is unclear for some thermograms.

	Bulk Onset (°C)	Spray-Dried 100% Lipid	Spray-Dried Lipid:Ca (2:1)
Lecithin	-17	-19	-13
Phosphatidylcholine	-12	-23	-8
DSPC	80	78	95

Though the addition of calcium showed increases in production yield and melting temperature; the unsaturated PCs yielded materials that were difficult to handle, very hydroscopic and unsuitable for inhalation aerosol applications. The sub-ambient melting temperatures as determined by DSC for the egg lecithin and egg phosphatidylcholine raw materials correlate well with their waxy, plastic appearance and poor handling behaviour. On the other hand, the DSPC possessed a high melting temperature, and yielded free flowing finely divided powders that could be handled under ambient conditions.

18. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.



Jeffry G. Weers

25-Nov-02

Date

CURRICULUM VITAE

Jeffry G. Weers

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SUMMARY

Director with ≈17 years of experience in colloid-based research and development. Extensive experience with a wide variety of colloidal systems including: micelles, microemulsions, emulsions, liposomes, microbubbles, foams, liquid crystals, suspensions, and aerosols. Demonstrated leadership skills in supervisory and matrix team environments. Have worked on high visibility technically challenging projects that are currently in various stages of development, from preclinical to post-approval. Innovative, accomplishment oriented. Holder of numerous patents, publications in refereed journals and presentor at scientific conferences. Section Editor and member of the Editorial Board for the journal *Current Opinion in Colloid & Interface Science*, Guest Editor for *Colloids and Surfaces*. Positive motivator and mentor with a reputation for developing people.

EDUCATION

Ph.D., Chemistry, University of California, Davis, CA (1985)
B.S., Honors in Chemistry, University of Puget Sound, Tacoma, WA. (1980)

PROFESSIONAL EXPERIENCE

INHALE THERAPEUTIC SYSTEMS INC., San Carlos, CA (1999-present)
Director of Advanced Particle Research, Technical Leader, PulmoSphere® Technology

Joined Inhale as part of the acquisition of the *PulmoSphere* technology. Led integration of *PulmoSphere* technology into Inhale's core business.

- Completed four Phase I clinical studies involving the PulmoSphere platform.
- Technical lead on business development trips that resulted in the signing of Chiron and Johnson & Johnson to multiproduct inhalation deals.
- Elucidated the effect of calcium ions on the solid state characteristics of PulmoSphere powders
- Developed the regulatory strategy for blowing agents in PulmoSphere products

ALLIANCE PHARMACEUTICAL CORP., San Diego, CA (1991-1999)
Research Fellow/Senior Research Fellow/Director/Senior Director of Exploratory Pharmaceutical Research

Successfully led the fundamental research group for a start-up biotechnology company. Directed research efforts towards the development of engineered particles for biomedical applications

- Lead inventor of novel metered dose inhaler and dry powder inhaler formulations based on engineered particles designed to be both hollow and porous.
- Co-inventor of several patents related to the delivery of drugs in perfluorocarbon continuous phases. Led early pharmaceutical and business development of Alliance's *PulmoSphere®* drug delivery program.

- Co-inventor of poloxamer-based thermoreversible gels for post-surgical adhesion prevention and delivery of medicaments to the gastrointestinal tract.
- Led successful formulation effort to eliminate complement activation in early ultrasound formulations.
- Co-inventor of gas emulsion (microbubble) formulation used as a contrast agent for diagnostic ultrasound procedures; the technology was licensed to Schering AG for $65 MM plus royalties; approved by in Jun-2002 by FDA for endocardial border delineation.
- Co-inventor of partial liquid ventilation (PLV). PLV has completed pivotal Phase III trials in adult patients suffering from acute lung injuries. No statistical significance was observed over conventional mechanical ventilation in the treatment of ARDS/ALI patients.
- Led basic research program aimed at understanding the mechanisms of perfluorocarbon emulsion coarsening (i.e. Ostwald ripening, coalescence).
- Lead inventor of the *Oxygent*™ (fluorocarbon-in-water emulsion) formulation currently in Phase III clinical trials.
- Headed a company-wide reformulation effort designed to eliminate biological side-effects observed in perfluorocarbon emulsion ("blood substitute") formulations. Efforts resulted in clinically significant improvements in febrile and thrombocytopenia responses relative to earlier formulations.

THE CLOROX COMPANY, Pleasanton, CA (1985-1990)
Scientist II, Senior Scientist

Initiated new projects involving mixed surfactant systems including the following:

- Developed thickened bleach solutions with worm-like cationic micelles. This technology is currently being used commercially in the *"Industrial Strength Liquid Plumr"* product.
- Developed a solvent-free cleaning technology based on mixed surfactants.
- Developed a spherulitic aqueous delivery system for lipase enzymes.
- Characterized micellar sphere to rod transitions in mixed surfactant systems via Fourier transform infrared spectroscopy, dynamic rheology, and tensiometry.

UNIVERSITY OF CALIFORNIA, Davis, CA (1981-1985)
Teaching Asst., Research Asst.

Thesis research involved examination of electronic energy transfer in organic and biological systems.

- Provided the first measurement of spin sublevel kinetics in triplet-singlet energy transfer processes.
- Showed that the spin sublevel selectivity in triplet-triplet energy transfer requires time for precession about the spin axis (a statement of the Heisenberg uncertainty principle).
- Examined energy transfer between tryptophan and heme groups in modified hemoglobins (pertinent to patients suffering from lead intoxication and erythropoietic protoporphyria).

PROFESSIONAL AFFILIATIONS

American Chemical Society
American Association of Pharmaceutical Scientists
International Society for Aerosols in Medicine
Controlled Release Society
Guest Editor for Colloids Surfaces A: Physicochemical and Engineering Aspects
Section Editor and member of the Editorial Board for Current Opinion in Colloid & Interface Science

PUBLICATIONS (58 total)

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